

NATIONAL INSTITUTES OF HEALTH  
NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL  
MINUTES OF MEETING

September 14, 2009

The 163rd meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) convened at 10:30 a.m. on Monday, September 14, 2009, in Conference Rooms E1/E2, Building 45, National Institutes of Health. Dr. Anthony S. Fauci, director, National Institute of Allergy and Infectious Diseases (NIAID) presided as chair.

In accordance with the provisions of Public Law 92-463, the meeting was open to the public from 10:30 a.m. to 11:40 a.m. and from 1:00 p.m. to 4:30 p.m. The meeting was closed to the public from 8:30 a.m. to 10:00 a.m. and from 11:40 a.m. to 12:00 p.m. for review and consideration of individual grant applications. Notice of the meeting was published in the *Federal Register*.

**Council Members Present:**

Dr. Ann Arvin  
Dr. Barbara Baird  
Dr. Carol Carter  
Dr. Satya Dandekar  
Dr. Sharon Kiely  
Mr. William McLin  
Dr. Louis Picker  
Dr. Regina Rabinovich  
Dr. Martin Rosenberg  
Dr. Marc Rothenberg  
Dr. Samuel Stanley  
Dr. Christel Uittenbogaart  
Dr. Christopher Walker  
Dr. Richard Whitley  
Dr. David Wilkes

***Ex Officio* Members Present:**

Dr. Mitchell Cohen  
Dr. Anthony Fauci  
Dr. Bruce Gellin  
Major General James Gilman  
Colonel Kent Kester  
Dr. Ronald Valdiserri

**Council Members Absent:**

Dr. Robert Brooks  
Dr. Kathryn Edwards  
Dr. Megan Sykes

***Ad Hoc* Members Present:**

Dr. Bjoern Peters

**NIAID Senior Staff Present:**

Dr. Hugh Auchincloss  
Dr. Carl Dieffenbach  
Dr. Carole Heilman  
Dr. Marvin Kalt  
Dr. Cliff Lane  
Dr. John McGowan  
Dr. Daniel Rotrosen

## **I. REVIEW OF GRANT APPLICATIONS**

The National Advisory Allergy and Infectious Diseases Council convened in closed session to consider applications in the areas of allergy and immunology, microbiology and infectious diseases, and AIDS.

Funding Actions: The Council reviewed 3,440 research and training applications with primary assignment to NIAID for a requested amount of \$466,899,617 in first-year direct costs and recommended approval of 530 applications for \$176,391,913 in first-year direct costs. Five Method to Extend Research in Time (MERIT) awards were recommended for approval.

## **II. REMARKS OF THE DIRECTOR, NIAID - Anthony S. Fauci, M.D.**

Dr. Fauci opened the Council session by welcoming visitors to the meeting. Drs. Kathryn Edwards and Megan Sykes were unable to attend the meeting, their last as members. Two other retiring members -- Drs. Barbara Baird and Martin Rosenberg -- were present to accept a plaque, certificate, and letter of appreciation for their service.

Dr. Fauci introduced one *ad hoc* Council member, Dr. Bjoern Peters, from the Vaccine Discovery Division at the La Jolla Institute for Allergy and Immunology. Major General Dr. James K. Gilman is the new Department of Defense *ex officio* member. He has delegated his Council subcommittee duties to Colonel Kent Kester, Walter Reed Army Institute of Research, who will be a member of the DMID subcommittee.

### **Consideration of Minutes of Previous Meeting**

Council considered the minutes of the May 18, 2009, meeting and approved them as written.

### **Nominations and Appointments by the Obama Administration**

Dr. Fauci announced a key nomination and appointment made by the Obama administration. On August 7, Dr. Francis Collins was confirmed as NIH director. In July, President Obama nominated Dr. Regina Benjamin as the next U.S. surgeon general.

Dr. Fauci noted that while awaiting Dr. Collins's confirmation, Drs. Raynard Kington and Lawrence Tabak led NIH capably. Dr. Kington, who served as acting NIH director since October, resumes his previous position as NIH's principal deputy director. Dr. Tabak, who served as acting deputy director, resumes his position as director of the National Institute of Dental and Craniofacial Research.

### **Staff and Organizational Changes**

Dr. Fauci announced that Dr. Diana Finzi was named the new chief of the Pathogenesis and Basic Research Branch in the Basic Sciences Program in the Division of AIDS.

Jennifer Compton was selected chief of the Workforce Management Branch, Office of Workforce Effectiveness and Resources.

## **Tributes and Awards**

Dr. Fauci congratulated four NIAID intramural scientists who were honored by and elected to the American Academy of Microbiology: Drs. Jonathan Yewdell, Jeff Taubenberger, Ed Berger, and Jack Bennink.

Dr. Fauci underscored how much those at NIH, and particularly those at NIAID, appreciate the life and work of Senator Ted Kennedy, an incredible friend of NIH throughout his long and historic career in public service. He was a committed and articulate proponent of the work NIH does, and his support and leadership helped advance biomedical research and public health.

## **Budget Update**

The president's FY 2010 budget request for NIH is \$30.8 billion, a 1.5 percent increase over FY 2009. The NIAID proposed allocation is \$4.76 billion, an increase of 1.2 percent over the FY 2009 appropriated level. Most of the increase for NIH is attributed to the president's goal of doubling the budget for cancer research over ten years. To accomplish this, various programs in the NIH Office of the Director were reduced. Each IC would get at least one percent in their FY 2010 budget when compared to the 2009 amount.

The House and Senate have marked up their own version of an FY 2010 appropriation for NIH. The House version provides a 3.1 percent increase while the Senate version provides 1.5 percent increase over the FY 2009 level. Congress rejected the administration's request to set a specific funding level for cancer research.

The final appropriations bill will be worked out in conference. Until the FY 2010 appropriations bills are signed, NIAID will be operating under a continuing resolution. The FY 2009 interim payline for R01 research project grants is the 6.0 percentile.

Dr. Fauci discussed the American Recovery and Reinvestment Act (ARRA) and its impact on NIAID. Out of the \$10.4 billion in ARRA funds allocated to NIH, NIAID received \$1.11 billion. More than 1,000 projects have been funded and \$370 million has been obligated. More than 70 percent of funds has been allocated to research project grants. ARRA monies have allowed the Institute to renew support of the National Emerging Diseases Research Network and to fund Regional Centers of Excellence for biodefense and emerging infectious diseases. Approximately \$100 million of the funding is being used for projects related to novel H1N1 influenza.

## **Legislative Update**

On May 21, 2009, Dr. Fauci accompanied Dr. Kington as he presented the FY 2010 NIH budget to the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education.

On June 1, Dr. Fauci was invited by the ad hoc group for medical research to participate in the first of a series of Congressional briefings on NIH's plan to use ARRA funding to help stimulate the economy and advance scientific and biomedical research.

On June 30, Dr. Fauci participated in a Congressional briefing on the 2009 H1N1 influenza outbreak entitled, "Learning to Live in a World With the H1N1 Pandemic." He described HHS's implementation activities under the National Pandemic Plan and updated Congressional staff on the status of vaccine development.

### **Other Information Items**

Dr. Fauci discussed swine flu and the work NIAID's grantees and contractors are doing in the areas of molecular analysis, pathogenesis, immune response, the evolution of the virus, and transmissibility studies.

Dr. Fauci also spoke about global health issues, such as tuberculosis and HIV/AIDS. Dr. Fauci attended the International AIDS Conference in Cape Town, South Africa, in July and visited several townships where the PEPFAR program is being implemented.

In other news, NIAID developed a consultation on developing clinical research infrastructure for infectious diseases for 2010 to 2020. The Institute has launched two new clinical trials aimed at prolonging the effectiveness of currently available antibacterial drugs, and it is funding a new human immune profiling research center.

### **III. GUEST SPEAKER – Dr. Kathryn Zoon, Director, NIAID Division of Intramural Research**

The Division of Intramural Research (DIR) has two important organizational changes. Dr. Patrick Duffy will head the Malaria Vaccine Development Branch. He comes from Seattle Biomedical Research Institute and is expected to start in November.

Gary Mays is the new associate director for Strategic Planning and Financial Management.

Dr. Zoon discussed DIR's budget, which has been flat for the last four years. With mandatory increases in salary and trainee stipends as well as a two to four percent increase in overhead, DIR expects a 2.7 percent decrease in all laboratory controllable budget items, such as supplies, services, and other contracts and equipment.

As far as ARRA funds, DIR initially received \$3 million for large-scale equipment, then received more monies for 2009 H1N1 studies.

Dr. Zoon outlined DIR's strategic priorities, including maintaining a robust portfolio of basic research for infectious diseases and immunology, and also completing activation of the biodefense and emerging infectious disease research programs. DIR is also emphasizing clinical research.

She announced personnel updates, including newly tenured as well as new tenure track investigators. DIR is conducting several searches to fill vacancies. The Laboratory of Infectious Diseases needs lab chiefs while the Laboratory of Immunology is seeking a tenure-track investigator. DIR will be recruiting one or two clinical research transition fellows for its clinical program, as well as one or two clinical tenure-tracks.

The Board of Scientific Counselors conducted its periodic review of DIR laboratories and programs. Almost all the labs reviewed received outstanding or excellent reviews.

Dr. Zoon also discussed facility changes and updated attendees on the International Centers for Excellence, which has a new program in Cambodia.

She concluded with an overview of DIR's influenza research program and the work of several DIR investigators.

**IV. REPORT OF THE DIVISION OF ALLERGY, IMMUNOLOGY AND TRANSPLANTATION COUNCIL SUBCOMMITTEE - Daniel Rotrosen, M.D., Director**  
**DAIT STAFFING/ORGANIZATIONAL CHANGES:**

Dr. Rotrosen opened the Subcommittee Council meeting by welcoming all returning members of the National Advisory Allergy and Infectious Diseases Council Subcommittee. Dr. Rotrosen also welcomed two *ad hoc* Council members, Drs. Alessandro Sette, and Bjoern Peters. It was related that the *ad hoc* Council members would be presenting talks to the Council members and staff.

Dr. Rotrosen informed the subcommittee members of two new staff members to the division: Dr. Jeffrey Rice joined the Division in May 2009 as a Program Officer in the Basic Sciences Section of the Transplantation Immunobiology Branch and Ms. Sherrie Pryber, BSN, MS, who joined the Clinical Immunology Branch in June 2009 as a Project Manager.

Dr. Rotrosen concluded his remarks by letting the subcommittee members know that members of the division's branches and offices had participated in a number of workshops, symposiums and meetings. In addition, the division had released several scientific initiatives.

Following Dr. Rotrosen's opening remarks he presented Drs. Peters and Sette from the La Jolla Institute for Allergy and Immunology who presented their respective works on "The Design of the Immune Epitope Database (IEDB) and Associated Analysis Resource" and "Populating the IEDB and Meta-analysis of Specific Diseases."

Dr. Rotrosen noted that several concepts will be presented for the Subcommittee's consideration. These concepts form the foundation for a number of the basic and clinical science programs of the division.

The following concepts were presented for the Subcommittee's consideration:

**Asthma & Allergic Diseases Cooperative Research Centers:** The initiative will support NIAID's unique and long-standing Asthma and Allergic Diseases Cooperative Research Centers (AADCRC) program, which funds research centers across the U.S. to conduct interdisciplinary and translational research in asthma and allergic diseases. The centers coordinate their efforts through a steering committee and collaborate with one another through a discretionary fund that supports small, independent pilot studies. The Subcommittee felt that this initiative provides a valuable resource and an important infrastructure to stimulate and advance research. The Subcommittee unanimously approved this initiative.

**Genomics of Transplantation:** This initiative will support a cooperative network of investigators from diverse backgrounds, including molecular biologists, population geneticists, immunologists, transplant clinicians, statisticians, and informatics specialists to conduct research directed at:

1. Pharmacogenetic analysis of microsatellite and single nucleotide polymorphisms (SNPs), as well as SNP haplotypes in candidate genes of both transplant donors and recipients, and correlation of these genetic variations with responses to, and outcomes of, immunosuppressive protocols.
2. Delineation of microsatellite polymorphisms, SNPs, and SNP haplotypes in candidate genes and identify unique gene expression patterns in minority populations who are at risk of lower graft survival.

3. Analysis of gene polymorphisms, cDNA microarrays, as well as proteomics to identify and characterize immune response genes expressed during acute and chronic graft rejection, that relate to onset and severity of graft rejection.
4. Statistical and database approaches to analyze multiple gene interactions.

These studies will utilize recipient and donor blood and tissue samples, as well as clinical information, from both retrospective and concurrent clinical trials in transplantation. The Subcommittee endorsed and unanimously approved this initiative.

**Nonhuman Primate Transplantation Tolerance Cooperative Study Group: Opportunities Pool**

**Expansion:** The goal of the Nonhuman Primate Transplantation Cooperative Study Group (NHPCSG) is to evaluate the safety and efficacy of novel tolerance-induction therapies in NHP models of kidney, islet, heart, and lung transplantation. In addition, the program supports research into the immunological mechanisms of tolerance induction and development of surrogate markers for induction, maintenance, and loss of tolerance. While the NHPCSG has many promising therapeutic strategies under study and in development, an opportunities pool (discretionary fund) allows newly identified tolerance-inducing therapeutics and strategies to be developed and evaluated in a timely manner prior to the conduct of clinical trials. The NHPCSG has a discretionary fund for pilot projects in islet and kidney models that are supported by the Congressional Special Appropriation for Type 1 Diabetes program. This additional funding for the discretionary fund will allow similar pilot projects using heart and lung models. This initiative also provides an opportunity for critical pre-clinical research to complement NIAID-supported transplantation clinical trials. The Subcommittee unanimously approved the initiative.

**Nonhuman Primate MHC Gene Discovery and Typing Technology Development:** The program's goal is to accelerate immunological research in nonhuman primate (NHP) models of vaccine and adjuvant development, infectious and immune-mediated diseases, and transplantation by 1) defining MHC alleles in multiple NHP species and 2) developing technologies for rapid high-throughput MHC typing. This initiative is a competitive renewal of the NHP MHC Discovery and Technology Development Program. It has three components: 1) gene identification and sequencing of the classical MHC loci and alleles in the most studied NHP species, 2) development of rapid, high-throughput MHC typing methods that can be easily adapted or utilized by NHP research laboratories, and 3) provision of MHC allele sequences, frequencies, and primers/probes required for typing or discovery to the NHP research community. The Subcommittee unanimously approved the initiative.

**NIAID Division of Allergy, Immunology, and Transplantation: Regulatory Management Center:**

The Regulatory Management Center will support DAIT's Office of Regulatory Affairs in activities required for conducting DAIT-supported clinical trials (including network- and consortia-conducted trials as well as investigator-initiated U01 trials) in the U.S. and elsewhere. The Center will provide regulatory and good clinical practice (GCP) compliance support for network and non-network trials that the Division supports. The scope of this contract will cover all trials whether conducted under health authority application or not. The centralized regulatory support initiative will facilitate the Division's ability to fulfill its responsibilities as a clinical trials sponsor to ensure: the safety and welfare of participants; adherence to applicable regulations, policies, standard procedures, required guidelines, and study protocols; and harmonization of processes across DAIT branches and programs to remove unnecessary redundancies of operations that will lead to ultimate cost savings. Subcommittee endorsed and unanimously approved this initiative.

**Protective Immunity in Special Populations:** This program will support contracts that characterize the immune response in immunocompromised groups and conduct mechanistic studies to determine how immune defects alter generation and maintenance of protective immunity to infection or vaccination. Proposals will utilize *in vitro* methods using human cells and appropriate *in vivo* animal models to conduct the mechanistic studies. Target study groups include: aging adults, neonates, infants and children under 5 years of age, pregnant women, and patients receiving immunosuppressive drugs for the treatment of autoimmunity or transplant maintenance. This solicitation will be an open competition, permitting applications from prior awardees and new applicants. Submission from incumbents will permit contractors to build on and accelerate recent progress. Proposals from new investigators open the door to examination of novel immune compromised populations and NIAID Category A, B, or C priority pathogens that were not previously supported. The renewal initiative has been changed to include mechanistic studies of immune defects in immune compromised populations. The population categories have also been narrowed to provide a stronger focus and more possibilities for interaction between the funded contractors. Additionally, this initiative will not support projects that propose methods for enhancing the efficacy of vaccination (which was solicited in the previous initiative) because current NIAID programs already serve this need. The Subcommittee unanimously approved the initiative.

**Immune Epitope Database and Analysis Program:** This initiative will support the continuation of the Immune Epitope Database and Analysis Resource (IEDB; [www.immuneEpitope.org](http://www.immuneEpitope.org)), a public Web site that houses a comprehensive database of antibody and T cell epitopes for emerging/re-emerging infectious diseases and immune-mediated diseases, with a focus on NIAID Category A-C priority pathogens. The IEDB Web site also houses a suite of antibody and T cell epitope prediction software and a suite of epitope analysis software tools. Only HIV epitopes are excluded from the IEDB, as they are covered by a separate NIAID-sponsored database devoted to HIV. There will be no major changes in the scope of the renewal. The main goals of the program will remain the same: 1) maintain and further develop a comprehensive public database of antibody and T cell epitopes for emerging/re-emerging infectious and immune-mediated diseases, 2) develop, support, and provide epitope prediction and analysis software tools to the research community, and 3) conduct community outreach to expand community awareness and usage of this resource, as well as solicit community feedback to improve the utility of this resource for the research community. However, the scope of T cell epitope prediction tools will be decreased to eliminate development of prediction tools for specific human and murine class I alleles, since adequate tools are available publicly. The Subcommittee unanimously approved the initiative.

## **V. REPORT OF THE DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES – Carole Heilman, Ph.D., Director**

Dr. Heilman welcomed new *ex officio* member, Dr. Kent Kester, who is the commander of the Walter Reed Army Institute of Research, and is also a staff physician at Walter Reed Medical Center. Dr. Heilman also recognized Subcommittee member Dr. Martin Rosenberg for his significant contributions during his tenure on the DMID Subcommittee, noting that this was his final session as a Council member. Dr. Heilman then referred to the Branch Chiefs/Acting Branch Chiefs in attendance to introduce their respective new hires.

In follow-up to the “Clinical Trial Planning Summit: Update,” presented by NIAID Deputy Director Hugh Auchincloss just prior to the DMID segment, Subcommittee members Drs. Ann Arvin and Sam Stanley expressed interest in learning more about the issues outlined by Dr. Auchincloss and requested

that they have the opportunity to contribute to future discussions on this topic. Dr. Heilman assured them that she would convey their request to senior NIAID leadership spearheading the effort.

Following Dr. Heilman's remarks, Dr. Michael Kurilla, Director of the Office of Biodefense Research Activities, reported on a recent program evaluation he and other DMID staff members conducted of the DMID Partnership Program, which supports early product development activities. This report provided background information for several of the concepts that were presented later during the Subcommittee session.

As background, DMID has been supporting the Partnership Program since 2002. Dr. Kurilla worked with program staff to analyze some of DMID's earlier partnership awards to determine how the candidate products supported through the program have fared as they have moved along the product development pipeline. The specific metrics evaluated included: receipt of follow-on funding from either private or public sources, technical validation, and manufacturability of the product. Dr. Kurilla provided examples of candidate products that had achieved success in each of these categories. He also noted that failure to achieve success in any of these categories was an important indicator and could help guide related research. Based on this assessment, it appears that the partnership program provides crucial scientific vetting that can evaluate the quality of potential candidate products between the basic research and more advanced stages of product development. Importantly, the program provides critical data that influence downstream development decisions both for that product and for other investigators operating in the same scientific area and making similar types of products.

The following concepts were presented for the Subcommittee's consideration:

#### **Partnerships for Next Generation Biodefense Diagnostics**

The objective of this concept is to support research that will facilitate the development of the next generation of non-nucleic acid amplification-based medical diagnostics that are anticipated to greatly improve a clinician's ability to rapidly diagnose and treat infectious diseases caused by priority pathogens. Specifically, this program will stimulate collaborative efforts and multidisciplinary approaches for early stage development of novel, emerging, innovative rapid, easy-to-use, sensitive and specific technologies for use in a clinical setting to pre-symptomatically and/or post-symptomatically diagnose infectious diseases caused by priority pathogens. The Subcommittee noted that while successful proof-of-concept technologies are not expected to be ready for validation studies (to enable FDA clearance) at the end of the project period, the initiative should state that FDA clearance would be an eventual long term goal of successful projects supported under this initiative. The Subcommittee also acknowledged that the initiative could provide an opportunity for researchers to apply novel technologies developed under DARPA-funded programs to detect NIAID Category A-C priority pathogens. The Subcommittee unanimously approved the initiative.

#### **Partnerships for Biodefense**

The objective of this concept is to support mid-stage development of vaccines, therapeutics, adjuvants and diagnostics for biodefense and emerging infectious diseases, including all activities beyond lead candidate identification (e.g., safety evaluation, stability testing, manufacturing, development, etc.), diagnostic assay development, or initial development of diagnostic platform technology. This program will support collaborative efforts and multidisciplinary approaches to advance candidate products or platform technologies through the product development pathway. The Subcommittee expressed enthusiastic support for this concept and agreed that this type of activity is needed to facilitate product development. One Subcommittee member recommended that the initiative be more targeted and inquired as to the long-

term objective of the partnership program. DMID stated that the partnership topic area(s) and product development stage of responsive projects are adjusted each year in response to progress arising from prior initiatives and program evaluations of needs. The objective of the program was stated to be facilitation of the advancement of candidate products towards Phase 1 trials. Another Subcommittee member expressed concern regarding support of biodefense-related products for which no, or a very small, market may exist. Dr. Kurilla responded that it is important to support these activities, including expansion of capabilities, in advance of a potential and unpredictable need. The Subcommittee unanimously approved this concept.

### **Partnerships for Development of New Therapeutic Classes for Select Viral and Bacterial Pathogens**

This concept would advance the development of new therapeutic classes for *C. difficile*, *N. gonorrhea*, and hepatitis B virus (HBV). It will promote new antimicrobial strategies based on recently generated biological and genomic data, and will support early to mid- stage product development, including all activities beyond target and candidate identification (e.g., selection and optimization of lead candidate, medicinal chemistry, assay validation, safety evaluation, stability testing, manufacturing, development, etc.). The Subcommittee expressed support for this concept commenting on the strong rationale for each of the organisms selected for inclusion. Members concurred that early to mid-stage development of novel therapeutic classes is the right place to focus efforts. It was noted that NIAID involvement may in fact help generate increased private sector response in these particular areas. The Subcommittee unanimously approved this concept.

### **Vaccine and Therapeutic Preclinical Services**

The objective of this concept is to provide a variety of IND-, BLA- and NDA-enabling activities including manufacturing (GMP, process development, formulation, stability, etc), pharmacology, immunogenicity, toxicity testing, product development planning, and assay development and validation. These preclinical services are intended to fill gaps in the product development path, not to support a comprehensive product development program. Services are available to investigators in academia, not-for-profit organizations, industry, and government worldwide. This program is part of DMID's new consolidated, integrated approach to the provision of preclinical services.

The Subcommittee expressed high enthusiasm for this concept. Members indicated that the resource is needed to fill gaps in the product development path for therapeutics and vaccines. Members acknowledged the success of the existing Therapeutic Preclinical Services contract, which will be recompeted under this initiative. The Subcommittee unanimously approved this concept.

## **VI. JOINT MEETING OF THE AIDS SUBCOMMITTEE, NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL AND AIDS RESEARCH ADVISORY COMMITTEE (ARAC) – Carl Dieffenbach, Ph.D., Director, DAIDS**

Dr. Carl Dieffenbach welcomed the ARAC members, attending DAIDS and NIAID representatives, and other guests. He explained that the formal ARAC meeting would be preceded by a presentation about progress in planning for new NIAID clinical trials research networks. He introduced Hugh Auchincloss, Jr., M.D., NIAID Principal Deputy Director, and H. Cliff Lane, M.D., NIAID Deputy Director for Clinical Research, who described that effort.

## **CLINICAL TRIALS PLANNING SUMMIT – UPDATE**

*Drs. Cliff Lane and Hugh Auchincloss*

Dr. Cliff Lane began by quoting Dr. Fauci, director, NIAID, who at the Pacific Health Summit in June 2009 noted that he was exploring the possibility of using the HIV/AIDS clinical trials networks to conduct clinical trials for tuberculosis and other infectious diseases. Toward that end, in July 2009, the institute hosted a retreat entitled NIAID Consultation on Developing Clinical Infrastructure for Infectious Diseases, 2010–2020. Dr. Lane described the meeting, which included three breakout sessions to discuss: (1) elements of successful clinical research (2) strengths and weaknesses of alternative research models for funding and conducting research and (3) international research issues. The different breakout groups began examining a variety of important issues, including among others, utilization of a central institutional review board (IRB) model; defining adequate oversight; simplifying adverse event reporting; achieving consistency across data and safety monitoring boards; varying strengths and weaknesses of domestic and international sites; aligning research with local needs and capabilities; partnering with other research funders and ensuring adequate administrative support.

Dr. Hugh Auchincloss stated that the research networks resulting from the planning process will be established through the recompetition of the Division of AIDS (DAIDS) HIV/AIDS Clinical Trials Research Networks. However, discussions will proceed rapidly to determine how the existing infrastructure of the research networks can be utilized more immediately to incorporate for other infectious disease research within the HIV/AIDS networks. Tuberculosis, Hepatitis C, and influenza will be prime candidates for the integration of research. While no decisions have been made about the exact nature of the recompetition, it has been determined the recompetition for the different areas of HIV/AIDS research, e.g., treatment, vaccine, prevention, microbicide, and pediatric research will be staggered. The retreat produced eight working groups focusing on the following topics:

- R34-U01 processes
- Immediate expansion of existing networks
- Barriers to clinical research
- Timelines for recompetition of HIV/AIDS clinical trials networks
- HIV/infectious disease therapeutics network
- Immune Tolerance Network (ITN)-like HIV/infectious disease network
- HIV/infectious diseases vaccine research network
- Special considerations in international research.

Representatives of the planning process will report back to Council after a planned retreat in the winter.

### *Discussion*

In response to the suggestion for a formal review of the efficacy of the existing research networks, it was noted that DAIDS is conducting an ongoing assessment of network productivity (for the current cycle). During the discussion, it was recommended that NIAID consider the dissatisfaction among extramural researchers about which trials are initiated within the networks and the process for which those decisions are made as they plan for the future. Dr. Auchincloss emphasized that expansion of the networks may help facilitate flexibility, increasing NIAID's ability to respond to research priorities as well as a broader range of research proposals. It was noted that various issues and barriers relating to the use of IRBs will have to be addressed. The program planners will also bear in mind the many activities that the HIV/AIDS clinical trials networks have performed well over the years and the infrastructure and processes that have supported those efforts.

## **DIRECTOR'S REPORT**

*Carl W. Dieffenbach, Ph.D., Director, DAIDS*

Dr. Dieffenbach presented a report on division activities. He announced the appointment of Diana Finzi, Ph.D., as Chief, Pathogenesis and Basic Research Branch in the Basic Sciences Program.

### *Budget Update*

Dr. Dieffenbach reported that President Obama presented his FY 2010 budget request to Congress in May. The request includes \$30.8 billion for the NIH (a 1.5-percent increase) including 4.8 billion for NIAID (a 1.2-percent increase). A House markup version of the budget features a 3.1 percent increase in the NIH budget, and a Senate version features a 1.5 percent increase. The president's budget reflects a goal of doubling the cancer research budget during the next 10 years, in part by making reductions in NIH Office and Director programs and ensuring that each institute and center receives an increase of at least 1 percent.

NIAID's FY 2010 fiscal policies will feature a conservative approach because of the new peer-review scoring system, which could result in fewer awards. Because of the uncertainty, NIAID is setting its interim R01 payline at the sixth percentile (10th percentile for new investigators). Paylines may rise later in the fiscal year.

Of its \$1.11 billion in funds from the American Recovery and Reinvestment Act (ARRA), NIAID has supported more than a thousand projects and has obligated \$300 million. More than 70 percent of those obligated funds has been allocated as research project grants (RPGs). NIAID has used ARRA funds to renew support for the National Emerging Diseases Research Network, to supplement the Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases, and to support projects related to H1N1 influenza. The funds are addressing NIAID's four signature projects—stopping the AIDS pandemic, protecting health using immunology and vaccines, developing partnerships and products for biodefense and emerging infectious diseases, and expanding research capacity (regional centers) for biodefense and emerging infectious diseases. ARRA funds have been used to provide payline extensions.

### *Scientific Update*

Dr. Dieffenbach reported on two large research studies – the VOICE study and the CIPRA Haiti study. The VOICE study (Vaginal and Oral Interventions to Control the Epidemic) opened in mid-August in Zimbabwe. It will examine whether antiretroviral medications used to treat HIV infection also can prevent HIV infection in women when applied in a vaginal gel or taken as oral tablets once daily. This phase-IIb study will involve 4,200 HIV-negative women in five African countries. Specifically, it will compare two approaches, an investigational microbicide gel containing tenofovir and a pre-exposure prophylaxis (PrEP) approach featuring tablets of tenofovir or tenofovir/emtricitabine.

The CIPRA-Haiti trial demonstrated that HIV-infected adults in a resource-limited setting are more likely to survive if they start antiretroviral therapy before their immune systems are severely compromised. Because of an immediate favorable result, the trial was stopped early. It underscores the importance of identifying HIV-infected people earlier in the course of the infection and starting ART sooner.

Dr. Dieffenbach announced that the division will be recompeting its DAIDS Research Support Services Project, a support contract that provides a wide range of management activities. The division will employ the Mission Oriented Business Integrated Services (MOBIS) schedule, which serves to compile a list of pre-selected qualified companies, streamlining the award process.

Finally, Dr. Dieffenbach expressed deep gratitude for the contributions of three members who are rotating off the ARAC—Wafaa El-Sadr, Brenda Lein, and Kathryn Edwards.

### *Discussion*

There was additional discussion regarding the subject of the clinical trials network plans, and issues of oversight and ethics were raised. Concern was expressed about the potential dilution of ongoing HIV/AIDS research with the addition of other infectious disease research. Dr. Dieffenbach emphasized the potential of the integration of research in both tuberculosis and hepatitis C would not dilute existing research as they are profoundly related to HIV/AIDS. The possibility of additional funds from other sources as a result of research expansion was also noted.

The new clinical trials program will require the establishment of leadership groups for disease areas and the determination of what should or should not be integrated to ensure efficiencies. As large ongoing trials are completed, existing resources and funds will be available and network resources and plans can be re-evaluated. It was suggested that NIAID map new networks to older network initiatives, including product development.

### **AIDS VACCINE RESEARCH SUBCOMMITTEE REPORT**

*Louis J. Picker, M.D., Vaccine and Gene Therapy Institute, Oregon Health Sciences University*

Dr. Picker reviewed the work of the ARAC's AIDS Vaccine Research Subcommittee. The subcommittee held a meeting in May 2009, during which the STEP trial, the HIV Vaccine Enterprise strategic plan, and the topic of eliciting broadly neutralizing antibodies against HIV were discussed.

Analysis of the STEP trial samples continues, with many different studies being conducted. Attendees of the May meeting discussed some of the scientific questions and issues (e.g., efficacy) that are emerging from the analyses. The work might suggest threshold immune responses for future vaccines. The STEP trial indicated that T-cell responses generated by the Merck vaccine did not correlate with the viral load setpoint. Studies have been carried out to determine the mechanism of enhancement observed in Ad5 seropositive individuals receiving the Merck vaccine. Two such studies have been published recently, both of which indicated that Ad5 status does not predict the Ad5 specific CD4 T-cell frequency or what happens after boosting with the vaccine. People who are Ad5 seronegative can have T-cell responses to common epitopes, indicating that Ad seropositivity may not be a good indicator of past adenovirus exposure. The trial results suggest topics for future studies, such as a possible viral sieve effect and phylogenetic clusters. Viruses infecting vaccines are more likely to have epitopes that differ from those in the vaccines, suggesting that the vaccine might block growth of some variants similar to the vaccine.

The May meeting featured many speakers on the topic of eliciting broadly neutralizing antibodies. In particular, they pointed out barriers to creating neutralizing antibodies. Many of the broadly neutralizing antibodies that have been identified are not representative of the primary antibody repertoire so the primary repertoire may need to be expanded. Another discussion of the meeting focused on modification of the B-cell response during HIV infection and pathogenesis, which may contribute to the difficulty in developing neutralizing antibodies.

These issues will continue to be discussed in the subcommittee meeting being held September 15.

## CONCEPT REVIEWS: PREVENTION SCIENCES PROGRAM

### **Microbicide Innovation Program for Topical Microbicides**

*Jim Turpin, Ph.D., Preclinical Team Leader, Prevention Research Branch*

This concept has the objective of supporting innovative and developmental research projects to advance the field of topical microbicides. It is an R21/R33 mechanism and a renewal. The first year cost is \$3 million for the R21 (2 years) and \$2 million for the R33 (3 years). It is anticipated that between 5 and 10 awards will be made. Dr. Turpin explained how the Microbicide Innovation Program (MIP), with its two-phase structure, will cast a wide net to capture novel and unique activities for the advancement of microbicides. He described a broader program for microbicide development, which begins with MIP and leads to the Microbicide Trials Network.

The MIP is a milestone-driven program, in which applicant milestones are used to enable the transition from the R21 phase to the R33 phase. A transition process focuses on the accomplishment of milestones, programmatic and scientific priorities, and available funds. Dr. Turpin described progress in the program to-date, in which about 50 percent of researchers have transitioned from the R21 to the R33 for the first 2 iterations of the program (MIP I and MIP II). The program has been used by investigators as a platform for subsequent funding (unsolicited R21s and R01s and topic specific RFAs).

The ARAC reviewers consider this a good concept and feel that it meets a critical need. They suggested shifting the focus toward other aspects of microbicide discovery and development, such as new formulations and models. In discussion, Dr. Turpin noted that the program will use a full peer review and special emphasis panel. The ARAC members expressed support for the concept, made a motion to approve it, and voted in favor.

### **Methods for Prevention Packages**

*Vanessa Elharrar, M.D., M.P.H., Prevention Science Program, DAIDS*

This concept has the objective of developing new research strategies that will facilitate the design and testing of combination interventions to reduce HIV incidence. It is a renewal and uses an R01 mechanism. There will be 4 to 6 awards each lasting 3 to 4 years. The first year's cost of the program is \$4 million. The Prevention Packages initiative is cross-cutting, supporting collaborations between behavioral and biomedical clinical scientists, epidemiologists, and clinical trial design specialists. Six grants have been awarded. The National Institute of Mental Health co-sponsors the RFA and has co-funded four of the grants. The work is being conducted in Lesotho, Botswana, Uganda, Malawi, Estonia, and North/South America.

The ARAC reviewers expressed enthusiasm for the multidisciplinary aspect of the program. They asked for an expanded rationale for renewal. It was noted that optimization of prevention for specific populations and settings must be updated continually as new interventions and strategies become available. The program can address additional risk groups and settings. The ARAC members wondered about extending the program to include biomedical combinations, such as vaccines. They made a motion to approve the program, and they voted in favor.

## **CONCEPT REVIEWS: VACCINE RESEARCH PROGRAM**

### **Integrated Preclinical/Clinical AIDS Vaccine Development Program**

*Michael Pensiero, Ph.D., Vaccine Research Program, DAIDS*

This concept has the objective of supporting all stages necessary for translating innovative vaccine concepts into clinical research studies. It employs the U19 mechanism and is a renewal. There will be one award with a duration of 5 years and a first year cost of \$3.5 million. The concept responds to the recommendation for a stronger focus on basic HIV vaccine research and the need for clinical research that addresses specific scientific needs, such as validated animal models. It will allow for the integration and iteration of basic preclinical and clinical HIV prophylactic vaccine research. The program will support a multidisciplinary consortium of experts in animal models, molecular biology, immunology, manufacturing, and clinical testing. The earlier history of the IPCAVD featured projects that were more product driven (e.g., clade B poxvirus). Current IPCAVDs are, for example, evaluating modified MVAs for improved immunogenicity and evaluating modified cell substrates to manufacture rMVAs.

The ARAC reviewers believe this program is necessary for the translation of promising vaccines from the academic environment to the clinic. They recognized and applauded the fact that the concept has been revised to focus on answering immunologic questions in humans. This newer concept is research driven, allowing vaccines to answer research questions. The reviewers suggested building flexibility/funding into the program in case more than one promising approach surfaces. In discussion it was emphasized that this is not strictly a product development grant, and sentiment for having the project alternate between the discovery and development was expressed. ARAC members made a motion to approve the concept, and they voted in favor.

### **Consortia for AIDS Vaccine Research in Nonhuman Primates**

*Nancy Miller, Ph.D., Preclinical Research and Development Branch, DAIDS*

This concept has the objective of further elucidating the viral and host events that occur in acute mucosal SIV infection and determining how those events can be halted or modulated by vaccine-induced responses. It is a new initiative, with a duration of 5 years, and uses the P01 mechanism. One award will be made, with a first year cost of \$5 million. The program responds to a need for increased effective use of nonhuman primate models for AIDS vaccine research. These models can be used to increase understanding of the viral and host events that occur in mucosal tissues at the earliest stages of infection, to reveal the mucosal immune responses generated by vaccines, and to discover mucosal responses that are effective at blocking initial infection, systemic spread, and pathogenic effects.

The initiative will support collaborative, multidisciplinary consortia of investigators making use of nonhuman primate models. Studies in nonhuman primate/SIV models will allow detailed investigations of questions about immune responses that are difficult to address in humans. Areas to be addressed include the following:

- Early events of SIV mucosal route infection
- Mucosal responses elicited by vaccines and their effects on early events
- Understanding nonpathogenic SIV infection in natural hosts
- Investigating virus-host models.

The applicants will be required to propose a collaborative research plan, including aspects of mucosal infection and vaccine-induced mucosal response, to establish a scientific committee to review progress

and suggest changes in direction, and to describe an external scientific advisory board to evaluate programs. The ARAC reviewers agreed on the importance of studying the mucosal sites and the difficulty of studying the interface in humans. They characterized the concept as timely and stressed the importance of the consortium idea. They expressed a hope that additional funds and projects might be supported in the future.

In discussion, it was noted that a special emphasis panel will be used for reviewing applications. Suggestions were made to include communications with microbicide investigators, development of technologies to measure mucosal responses to virus exposure that could be utilized in human studies, and focus on early events in vaccination. The ARAC members made a motion to approve the concept, and they voted in favor.

Dr. Dieffenbach asked the ARAC members to consider areas of focus for upcoming meetings. He noted that some large prevention trial results will be released soon and can be discussed in January. It was also suggested that the committee have a discussion of strategies to apply when one or more prevention measures are found to be effective. Two other suggested areas of discussion included the economics of research and the broad area of drug resistance.

## **VII. ADJOURNMENT**

The meeting of the Council was adjourned at 3:53 p.m., on Monday, September 14, 2009.

We do hereby certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.

                  -s-                    
Anthony S. Fauci, M.D.  
Chairman, National Advisory Allergy  
and Infectious Diseases Council  
Director, National Institute of Allergy  
and Infectious Diseases

                  10/23/2009                    
Date

                  -s-                    
Marvin R. Kalt, Ph.D.  
Executive Secretary  
National Advisory Allergy and Infectious  
Diseases Council  
Director, Division of Extramural Activities  
National Institute of Allergy and Infectious  
Diseases

                  10/20/2009                    
Date

These minutes will be formally considered by the Council at its next meeting; any corrections or notations will be incorporated in the minutes at the meeting.